The Influence of Baseline Severity on Efficacy of Escitalopram and Citalopram in the Treatment of Major Depressive Disorder: An Extended Analysis

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Original Paper

Objective: To determine the differences between escitalopram and citalopram in the treatment of patients with major depressive disorder across a range of baseline severity of depression using trend analysis. **Methods:** Data from the three placebo-controlled studies comparing escitalopram to citalopram were analyzed. The pre-specified primary outcome variable was MADRS total score; secondary outcomes included Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I) scores. All analyses were based on an intent-to-treat (ITT) population and all direct comparisons were done by ANCOVA adjusting for baseline value and centre. **Results:** Analyses of the pooled data (N = 1203) show that, while the difference between citalopram and placebo was approximately constant across the range of baseline severity, the difference between escitalopram and placebo ($p = 0.0010$ for no trend) and between escitalopram and citalopram ($p = 0.0012$ for no trend) became greater, the more severely depressed the patients were at baseline. A similar pattern was apparent with the CGI-S and CGI-I results. There was a significant superiority of escitalopram over citalopram in response rate (defined as $\geq 50\%$ decrease in MADRS total score), and this difference increased with increasing baseline severity. **Conclusion:** These trend analyses thus indicate that the superiority of escitalopram over citalopram is more apparent as the baseline severity of depression increases.

Introduction

Several selective serotonin reuptake inhibitors (SSRIs) are currently available for the treatment of depressive and anxiety disorders, but it has been difficult to differentiate one from the other on the basis of measures of efficacy. Recently, however, accumulating evidence has suggested that escitalopram may have enhanced efficacy relative to other SSRIs [4, 5, 7].

Early studies on escitalopram used citalopram as an active comparator and, although these studies were not designed to detect differences between the two medications, escitalopram was found to be superior on some analyses of efficacy outcomes [3, 6, 11]. In two of the three placebo-controlled studies, the escitalopram groups separated from placebo on the pre-defined primary outcome measure (mean change from baseline in Montgomery–Åsberg Depression Rating Scale [MADRS], [9] total score) significantly earlier than the first point of separation of citalopram from placebo. In fact, in one of the studies [6] there was no separation in change in mean MADRS total score between citalopram and placebo at any time point during the 8-week treatment period, while in another [11] the citalopram group separated from placebo only at week 8.

When the data from the three 8-week, placebo-controlled studies were pooled (N = 1321), both escitalopram and citalopram significantly improved depressive symptoms (i.e. mean change in MADRS scores from baseline) compared with placebo [4]. Escitalopram produced a statistically significant improvement relative to placebo after 1 week of treatment and maintained that advantage at every study visit through to the end point. In contrast, citalopram treatment was not statistically superior to

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Table 1 Overview of included studies

	Burke et al. 2002 [3]	*Lepola et al. 2003 [6]*	*Rapaport et al. 2004 [11]*
Treatment duration	8 weeks	8 weeks	8 weeks
Treatment groups (average doses in brackets)	[ESC 10 mg] ESC 20 mg CIT 40 mg PBO	ESC 10–20 mg (14.0 mg) CIT 20–40 mg (28.4 mg) PBO	ESC 10–20 mg (17.6 mg) CIT 20–40 mg (35.3 mg) PBO
Dosing	Fixed	Flexible	Flexible
Baseline severity	MADRS ≥ 22	$22 \leq$ MADRS ≤ 40	MADRS ≥ 22
Setting	Specialist in US	GP in Canada, EU	Specialist in US

ESC, escitalopram; CIT, citalopram; PBO, placebo; MADRS, Montgomery–Åsberg Depression Rating Scale score; US, United States; GP, general practice (primary care); EU, European Union

placebo until weeks 6 and 8. Additionally, escitalopram treatment was significantly superior to citalopram in improving MADRS scores at week 1 in both last-observation-carried-forward (LOCF) and observed-case (OC) analyses.

The superiority of escitalopram was noticeable in the subset of patients that were more severely depressed, defined as those having a baseline MADRS score of 30 or greater [8]. In these patients (N = 506), escitalopram showed significant superiority to citalopram in reducing MADRS scores and in clinical response rates (56 % *vs* 41 %, respectively, $p < 0.05$) at week 8.

Given that the superiority of escitalopram over citalopram was more apparent when the patients were split into higher and lower severity groups, it would be of interest to determine the differences between escitalopram and citalopram across a range of baseline severity. The objective of this study was to examine this question using trend analysis, based on a linear relationship for response between baseline MADRS total score and treatment.

Methods

Studies: Doses and settings

There were three placebo-controlled studies comparing escitalopram to citalopram in the Lundbeck clinical trials database (described in detail in [1]; all studies were funded by H. Lundbeck A/S or Forest Laboratories Inc. Briefly, the studies were of multi-centre, randomized, double blind design (Table **1**), and recruited patients with moderate to severe major depressive disorder. Two involved psychiatric clinic settings while the other involved primary care settings. The pre-specified primary outcome variable was the adjusted mean change from baseline in total score on the MADRS; secondary outcomes included scores from the Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I) scales, and the Hamilton Depression Rating scale (HAMD). Response was prospectively defined as 50 % or greater reduction in MADRS total score. Remission was defined as a final MADRS score of 12 or less.

Statistics

All analyses were based on an intent-to-treat (ITT) population (i.e. , patients with at least one dose of study drug and one valid post-baseline efficacy assessment). All direct comparisons were done by ANCOVA adjusting for baseline value and centre.

In order to compare equivalent doses from the trials containing the same amount of the therapeutically active enantiomer [(*S*)-citalopram], data from the escitalopram 10 mg/d group of Burke et al. (2002 [3]) were not included in the analyses. The exclusion of this treatment arm did not affect the results in the total ITT population, but it resulted in an increased (without affecting the statistical significance) difference between escitalopram and citalopram for severely depressed patients (defined as patients with a baseline MADRS score ≥ 30) [1, 4, 8].

A trend analysis was conducted by examining the interaction between effect of treatment and severity at baseline as tested in an ANCOVA model, adjusting for baseline severity, centre, and treatment. This was done for escitalopram *vs* placebo, citalopram *vs* placebo, and for escitalopram *vs* citalopram.

In order to make a graphical presentation of the increasing effect with higher severity, the data were also analyzed by increasingly severe subgroups, each step increasing by 2 points on the MADRS total score. For each subgroup, treatment estimates and confidence intervals were calculated by ANCOVA and plotted.

Results

Disposition and Demographics

Table **2** presents the patients' disposition, demographics, and mean baseline MADRS total score for the three studies. There were no significant differences between treatment groups in age or mean MADRS total score at baseline.

Outcome at the end of study, by baseline severity

Analysis of the pooled data show that, while the difference between citalopram and placebo was approximately constant across the range of baseline severity, the difference between escitalopram and placebo ($p = 0.0010$ for no trend) and between escitalopram and citalopram ($p = 0.0012$ for no trend) became greater for the more severely depressed patients at baseline (Fig. **1A** and **1B**). For example, for patients with a baseline MADRS score of ≥ 35, the differences between escitalopram and placebo and between escitalopram and citalopram were about 6 points on the MADRS scale. These differences were not the result of a dosage bias, since the mean daily dose at last assessment was 16.8 mg for escitalopram and 33.7 mg for citalopram for patients with a baseline MADRS total score of < 30, and

Table 2 Patient disposition, demographics, and mean baseline MADRS total score for the 3 studies

	Lepola et al. 2003 [6]			*Burke et al. 2002 [3]*				*Rapaport et al. 2004 [11]*		
	PBO	*ESC 10-20*	*CIT 20-40*	*PBO*	*ESC 10*	*ESC 20*	*CIT 40*	*PBO*	*ESC 10–20*	*CIT 20–40*
ITT (N)	154	155	159	119	118	123	125	125	124	119
Females (%)	72	75	69	59	71	67	62	58	52	49
Age (years ± SD)	43 ± 12	43 ± 11	44 ± 11	40.3 ± 10.6	40.6 ± 12.3	39.6 ± 12.1	40.0 ± 11.5	42.2 ± 12.5	41.4 ± 11.9	42.1 ± 12.7
MADRS (mean ± SD)	28.7 ± 4.0	29.0 ± 4.3	29.2 ± 4.2	29.5 ± 5.0	28.0 ± 4.9	28.9 ± 4.6	29.2 ± 4.5	28.8 ± 5.0	28.7 ± 4.3	28.3 ± 5.0

MADRS, Montgomery-Åsberg Depression Rating Scale; ESC, escitalopram; CIT, citalopram; PBO, placebo; ITT, intent to treat population; SD, standard deviation

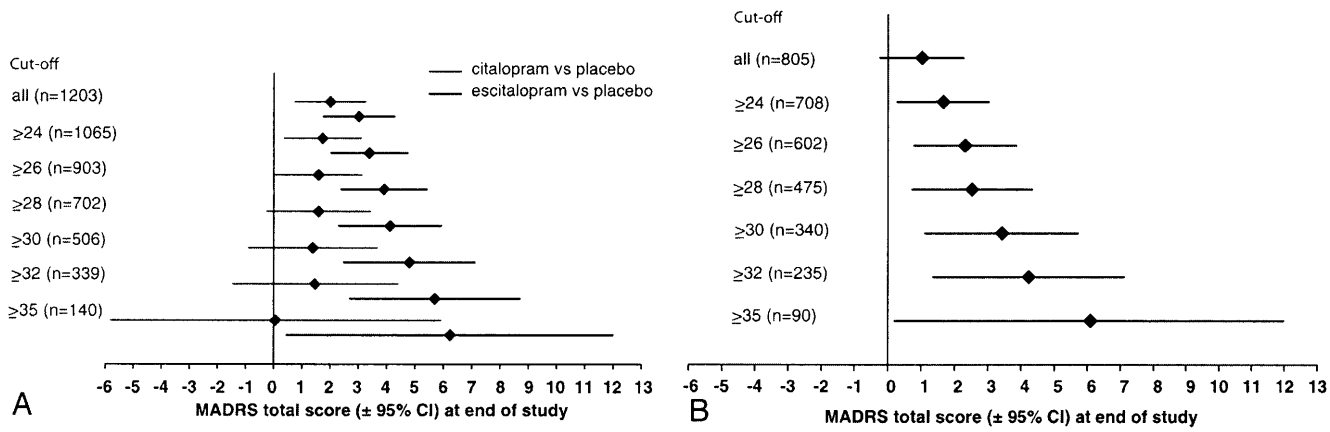

Fig. 1 Meta-analysis of the change from baseline in mean MADRS total scores (± 95 % CI) after 8 weeks of treatment with (A) escitalopram and citalopram *vs* placebo (p = 0.0010 for no trend between escitalopram and placebo, p = 0.9741 for no trend between citalopram and placebo) and (B) escitalopram *vs* citalopram (p = 0.0012 for no trend between escitalopram and citalopram), by baseline severity (according to total MADRS score).

16.8 mg for escitalopram and 34.4 mg for citalopram for patients with a baseline MADRS total score of ≥ 30.

To investigate the relationship between escitalopram dose and baseline severity, data from Burke et al. (2002 [3]) were analyzed. The effect of escitalopram 20 mg *vs* placebo increased with increasing baseline severity (p = 0.0033 for no trend), while this interaction failed to reach statistical significance for either escitalopram 10 mg or citalopram 40 mg *vs* placebo. Furthermore, the effect of escitalopram 20 mg *vs* 10 mg escitalopram significantly increased with increasing baseline severity (p = 0.0382 for no trend).

For the CGI-S, the difference between citalopram and placebo became smaller with increasing severity. However, the difference in CGI-S between escitalopram and placebo (p = 0.0047 for no trend) and between escitalopram and citalopram (p = 0.0004 for no trend) became greater the more severely depressed the patients were at baseline (Fig. **2A** and **2B**). A similar pattern was apparent with the CGI-I results, where an increased difference between escitalopram and placebo (p = 0.0013 for no trend) and between escitalopram and citalopram (p = 0.0020 for no trend) was observed with increasing baseline severity.

The same results were found with the HAMD-17 scores: the difference between escitalopram and placebo (p = 0.0341 for no trend) and between escitalopram and citalopram (p = 0.0014 for no trend) became greater the more severely depressed the patients were at baseline (data not shown).

Response to treatment

When the pooled data were examined by baseline severity, escitalopram had significantly higher response rates (defined as ≥ 50 % decrease in MADRS total score) at week 8 compared to placebo over the whole range of baseline severity (Fig. **3**). While there were no significant differences in response rate between escitalopram and citalopram in the patients with less severe depression at baseline, there was a significant superiority of escitalopram over citalopram with increasing baseline severity.

Discussion

These extended trend analyses from the pooled placebo-controlled studies of escitalopram *vs* citalopram indicate that the superiority of escitalopram becomes more apparent as the baseline severity increases. In less severely depressed patients, escitalopram and citalopram at equivalent doses have approximately similar efficacy, and both are significantly superior to placebo in depressed patients. However, the efficacy of escitalopram is increasingly significantly superior to placebo in reducing mean depression scores as the baseline severity of depression increases, and produces higher clinical response rates.

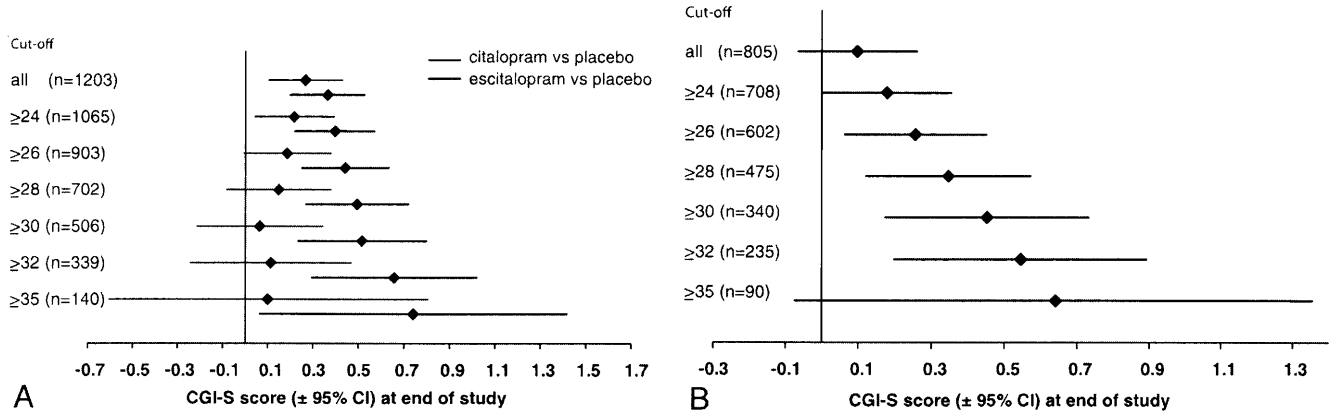

Fig. 2 Meta-analysis of the mean CGI-S scores (± 95% CI) after 8 weeks of treatment with (A) escitalopram and citalopram *vs* placebo ($p = 0.0047$ for no trend between escitalopram and placebo, $p = 0.4602$ for no trend between citalopram and placebo) and (B) escitalopram *vs* citalopram ($p = 0.0004$ for no trend between escitalopram and citalopram), by baseline severity (according to total MADRS score).

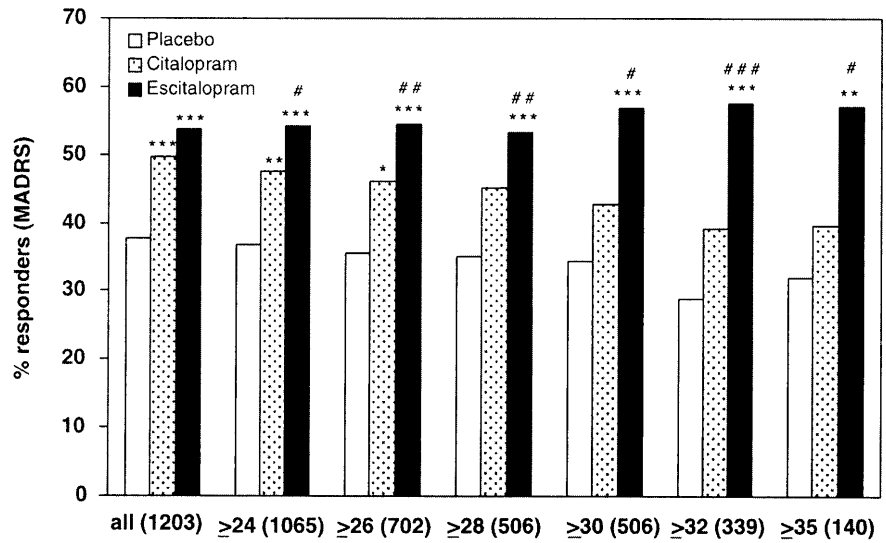

Fig. 3 Meta-analysis of the response (defined as ≥50% decrease in MADRS total score) after 8 weeks of treatment with escitalopram *vs* citalopram, by baseline severity (according to total MADRS score; number of subjects in brackets). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ *vs* placebo; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ *vs* citalopram.

This finding that escitalopram is superior to citalopram in more severely ill patients is consistent with other studies and meta-analyses that examined the influence of baseline severity. Two pooled analyses using all three placebo-controlled studies of escitalopram *vs* citalopram [8] and two placebo-controlled trials [7] both found that the severely ill group (baseline MADRS score ≥30) showed greater reduction in MADRS scores and higher response rates with escitalopram compared to citalopram. A quantitative meta-analysis [1] of four randomized controlled trials of escitalopram and citalopram compared baseline severity divided into four groups based on the MADRS: scores of <25, 25–30, 30–35, and >35. The two more severely ill groups (30–35 and >35) showed superiority of escitalopram compared to citalopram in MADRS change from baseline.

Bech et al. [2] examined escitalopram dose-response by re-analyzing data from the Burke et al. [3] study, in which two doses of escitalopram, 10 mg/d and 20 mg/d, were compared to citalopram 40 mg/d and placebo. They found that in the overall sample (N = 485), there was no difference in standardized effect size between the two doses of escitalopram. However, in the severely ill group (MADRS score ≥30, N = 212), there was a clear dose-response after that escitalopram 20 mg/d was superior in standardized effect size to both escitalopram 10 mg/d and citalopram 40 mg/d. In fact, the standardized effect size for escitalopram 20 mg/d (0.71) was larger than that found in other studies of citalopram.

The superiority of escitalopram is shown in an 8-week prospective study of escitalopram *vs* citalopram in patients (N = 280) with more severe depression at baseline (entry MADRS ≥30; mean baseline MADRS score = 35.7 ± 4.4) [10]. That study found that escitalopram 20 mg/d was superior to citalopram 40 mg/d in reducing MADRS scores at endpoint. Escitalopram also produced significantly higher response rates (defined as greater than 50% reduction in MADRS score at endpoint) than citalopram (76.1 *vs* 61.3%, respectively, $p < 0.01$). Similarly, escitalopram 20 mg/d was also superior in achieving remission (defined as final MADRS score ≤12) compared to citalopram 40 mg/d (56.1 *vs* 43.6%, $p < 0.05$).

In summary, several randomized controlled trials and pooled analyses have shown superiority of escitalopram over citalopram, especially in patients with higher levels of symptomatol-

ogy. This analysis indicates that patients with higher baseline levels of severity will show better response on a higher (20 mg/d) dose of escitalopram. Of note is that there are no controlled studies of escitalopram using doses higher than 20 mg/d. Future studies could examine whether higher escitalopram doses have greater efficacy, especially in the more severe population.

Acknowledgements

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